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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,530	05/24/2006	Meerpoel Lieven	PRD-2172USPCT	4231

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PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

EXAMINER

O DELL, DAVID K

ART UNIT	PAPER NUMBER
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1625

MAIL DATE	DELIVERY MODE
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05/08/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/580,530	Applicant(s) LIEVEN ET AL.	
	Examiner David K. O'Dell	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 March 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8 and 10-15 is/are pending in the application.
- 4a) Of the above claim(s) 10-15 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>5/24/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This application is a 371 of PCT/EP04/53280 filed 12/06/2004 and claims priority to (EPO) 03104601.4 filed 12/09/2003.

Claims 1-8, 10-15 are pending.

2. ***Response to Election/Restriction***

Applicant's election with traverse of Group I and the species compound 1 in the reply filed on March 25, 2009 is acknowledged. The traversal is on the ground(s) that no search burden exists. This is not found persuasive because the examiner stated (Restriction Election Requirement): "Because these inventions are independent or distinct for the reasons given above **and** there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art due to their recognized divergent subject matter, restriction for examination purposes as indicated is proper." (Emphasis added). Applicant should be reminded that the determination of the novelty of the compounds is only part of the examination process and the application requires the careful consideration of all statutes, requiring multiple searches. The examination of the method claims would require the consideration of non-prior art issues and the search of the relevant medical literature. This application contains claims drawn to a nonelected invention with traverse. A complete reply to this action must include a cancellation of nonelected claims or other appropriate action.

Under examination:

Group I, Claims 1-8, drawn to compounds and compositions and methods of preparing said compositions. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

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Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meerpoel, WO 2002081460 A1 (cited on the IDS), in view of Daugan, WO 2003048121 (cited on the IDS), Daugan, WO 2000032582 (U.S. equivalent is 6,552,022), Dodic, WO 2001096327 (cited on the IDS), Daugan, WO 2001097810 in further view of Williams et. al. “Novel Microsomal Triglyceride Transfer Protein Inhibitors” Expert Opinion On Therapeutic Patents 2003, 13, 479-488.

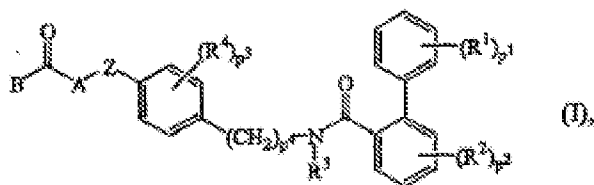
The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determination of the scope and content of the prior art

(MPEP 2141.01)

Meerpoel teaches the following genus of compounds:

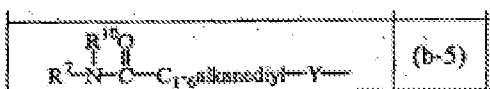
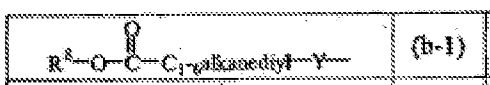
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Z is piperidine

X^1 and X^2 are each independently selected from CH, N or an sp^2 hybridized carbon atom and in radical (a-1) at least one of X^1 or X^2 is N;

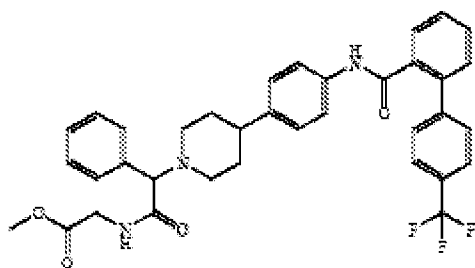
B represents a radical of formula



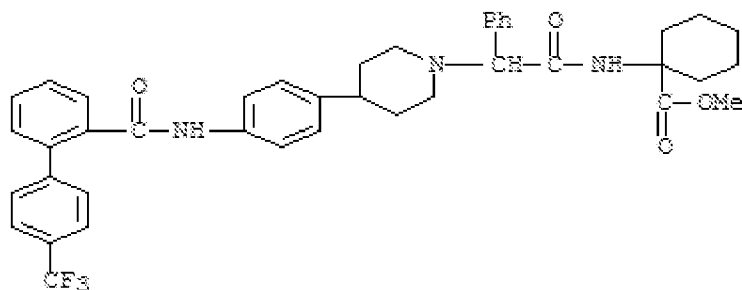
And B represents various amino acid residues.

A is an alkylene

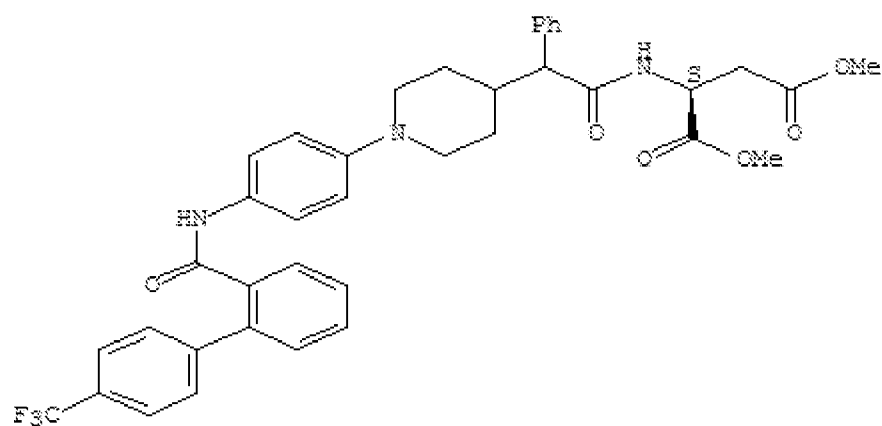
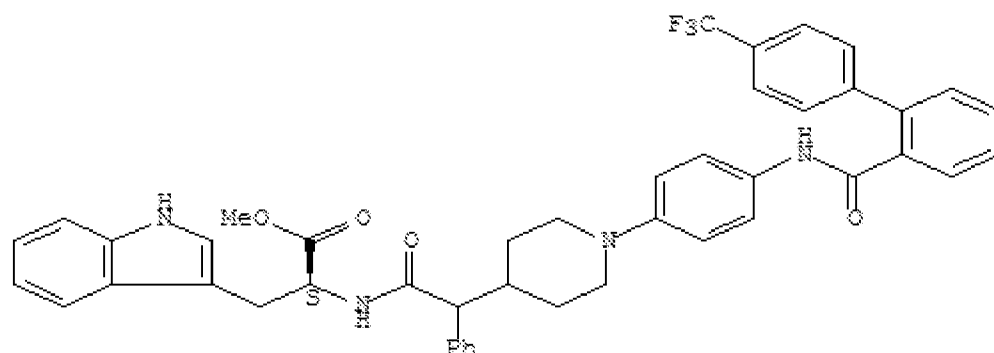
This genus is supported by numerous working examples, some of which are shown below:



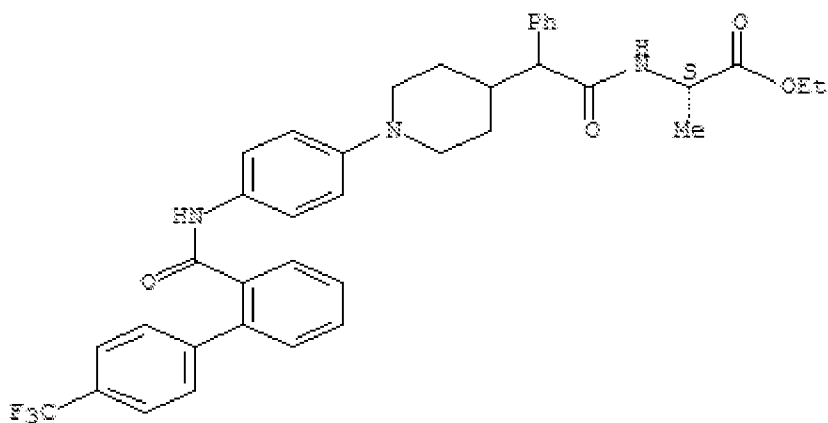
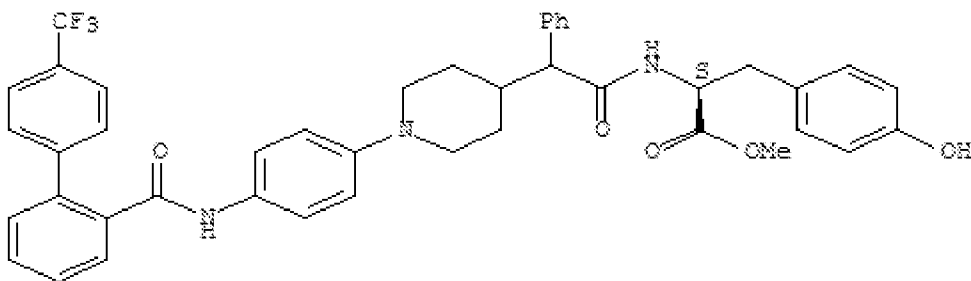
Ex. B.5



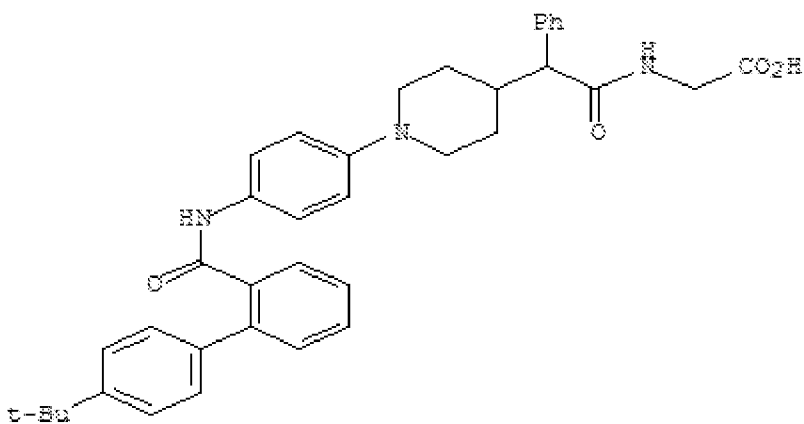
Art Unit: 1625



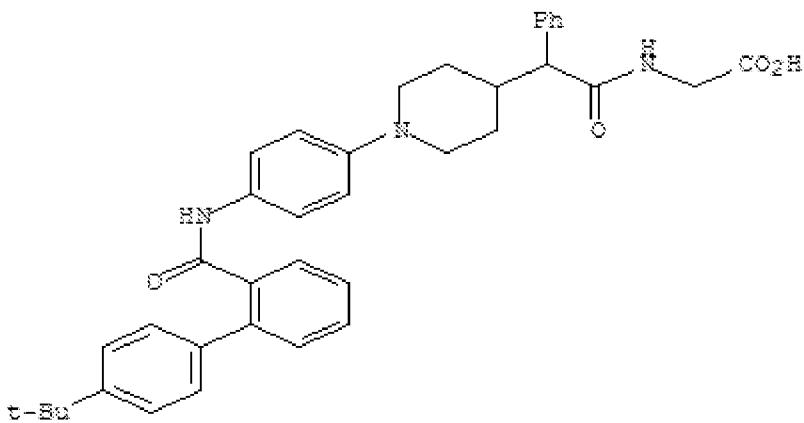
Art Unit: 1625



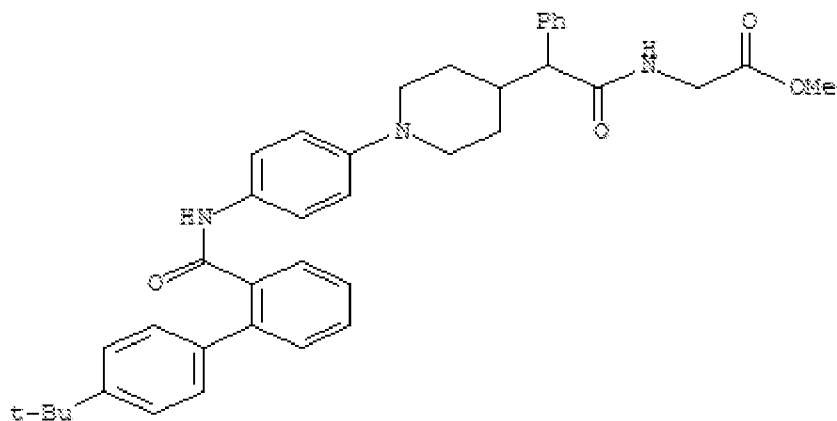
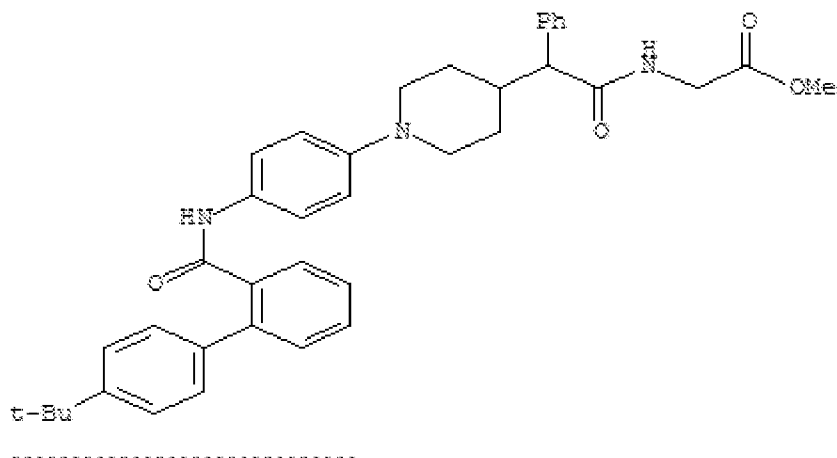
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Chemical structure of the compound



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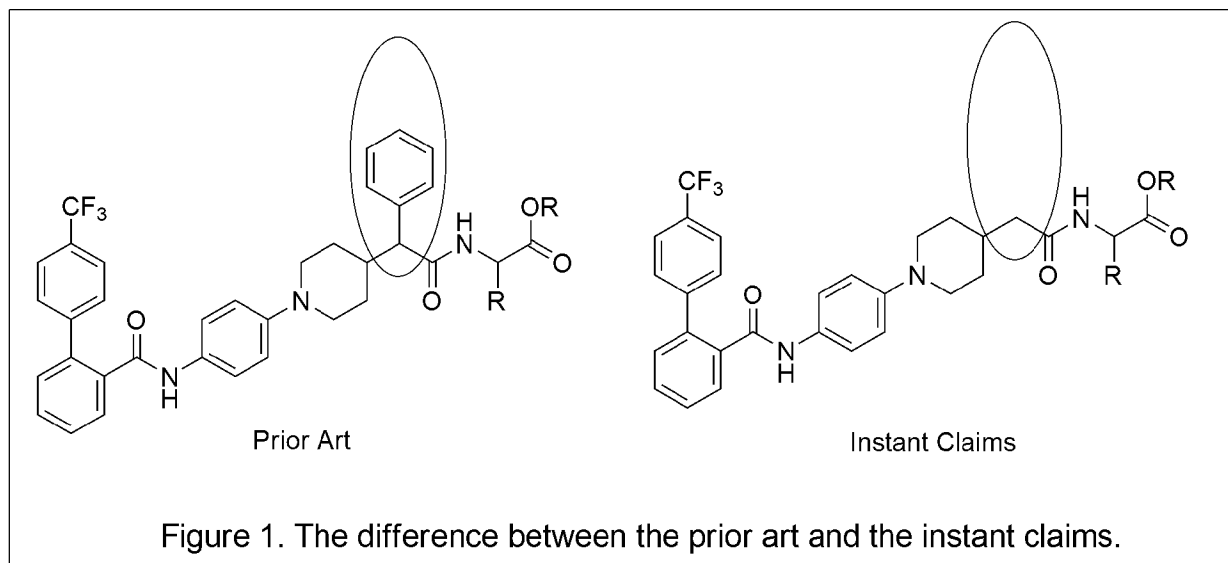


Ascertainment of the difference between the prior art and the claims

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All of the prior compounds are inhibitors of MTP/ApoB, which is the exact same utility of the instant case. This genus of WO 02081460 is essentially the same as the instant claims, but differs only in that a methylene linker is not exemplified in the particular compounds prepared. This species of the instant claims naturally read on the prior art genus.

The instant species differ from the prior art species, by removal of a phenyl, i.e. replacement of a benzyl radical with methylene. The difference between some relevant species and the prior art is shown graphically in Figure 1, below:



C) Resolving the level of ordinary skill in the pertinent art.

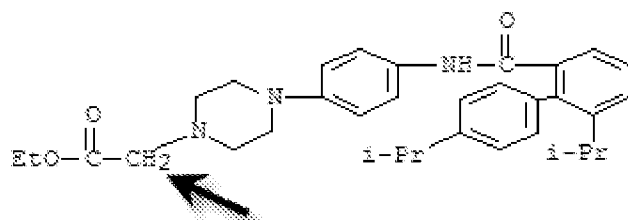
The level of ordinary skill is high. Someone preparing these compounds would be trained in organic and medicinal chemistry and would recognize the very close structural similarity and would expect them to have similar properties. It would be routine for a chemist to prepare species falling within the genus of the prior art, and close analogs.

D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

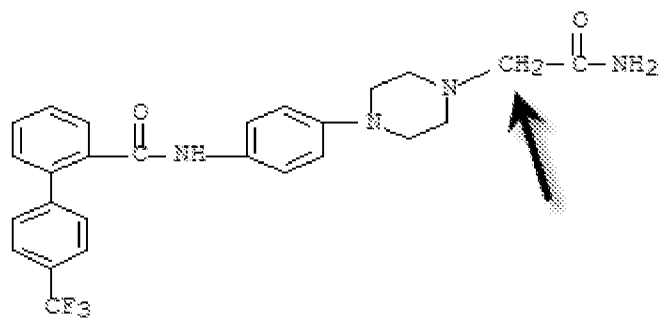
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Ordinarily it may not be obvious to remove a phenyl ring, and replace it with a methylene because such a change might be expected to alter pharmacological properties drastically, however the teachings of the secondary references show the methylene linker between the piperidine/piperazine MTP/ApoB pharmacophore to the amide or ester moiety. This can be seen in the following exemplified compounds of the relevant documents.

Daugan, WO 2003048121

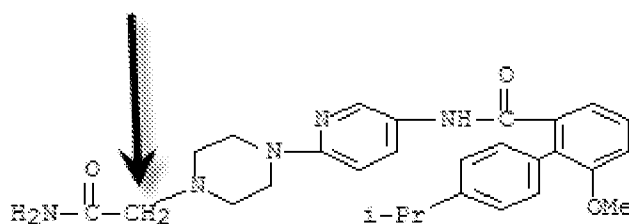
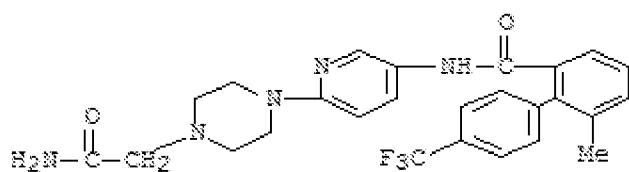
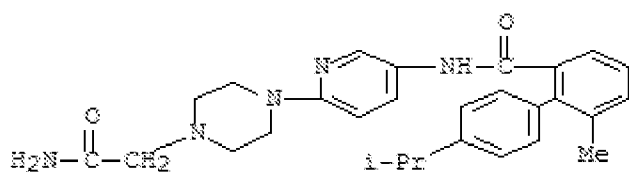


Daugan, WO 2000032582

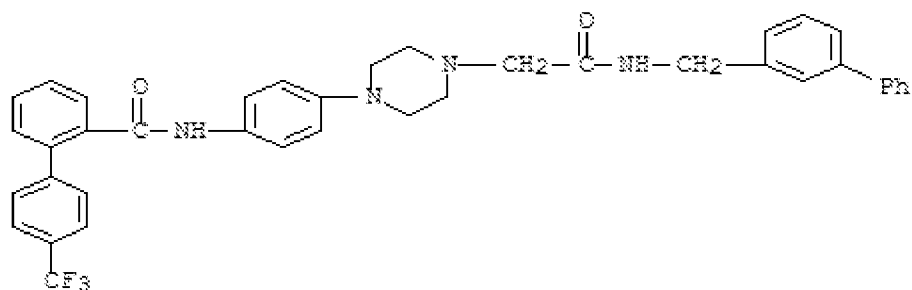


Dodic, WO 2001096327

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Daugan, WO 2001097810



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The Williams reference discusses the development of MTP ligands that have substantially the same core, that of a 2-phenylbenzamide, in section 6.2 pg. 482-484. It is clear from this discussion and the drawings of the active compounds, i.e. the structures 7-21, that the key structural feature is a 2-phenylbenzamide, and the other portion may be highly variable. There is a strong motivation in drug design to reduce the molecular weight of a drug in order to increase oral bioavailability. It is fairly common to systematically deconstruct a lead compound to find out which fragments are required for binding. In the instant case the prior art points directly to removal of the phenyl ring as shown by the secondary teachings. The genus of the prior art embraces the instant claims as well.

The compounds of the instant case are analogs of old compounds. One of ordinary skill would be motivated to make the compounds of the invention because he would expect the compounds to have similar properties and increased potency and selectivity. Indeed we see that these compounds have similar properties as those described by Shen. *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its **analogs** or isomers, either geometric isomers (*cis v. trans*) or position isomers (emphasis added) (*e.g. ortho v. para*)". The compounds are so close that a finding of anticipation might be made, however since no species were shown in the prior art that precisely fit the formula as presented an obviousness determination has been made. It is very clear based on the teachings of the prior art that the invention is obvious over the prior art.

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4. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meerpoel US PG Pub 2006/0040989 in view Meerpoel, WO 2002081460 A1 (cited on the IDS) in further view of Williams et. al. "Novel Microsomal Triglyceride Transfer Protein Inhibitors" Expert Opinion On Therapeutic Patents 2003, 13, 479-488.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

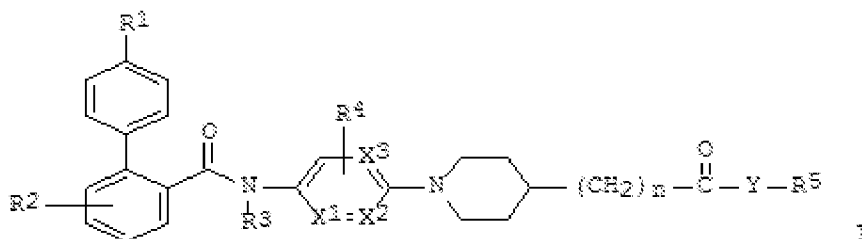
The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determination of the scope and content of the prior art

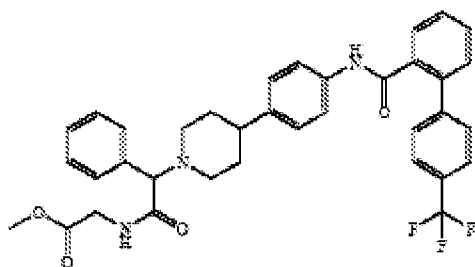
(MPEP 2141.01)

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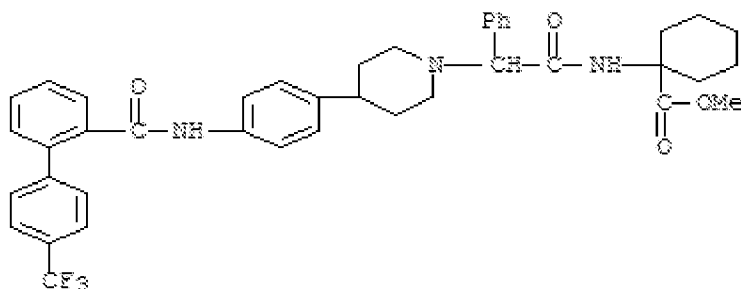
Meerpoel PG Pub 2006/0040989 teaches the following genus of compounds:



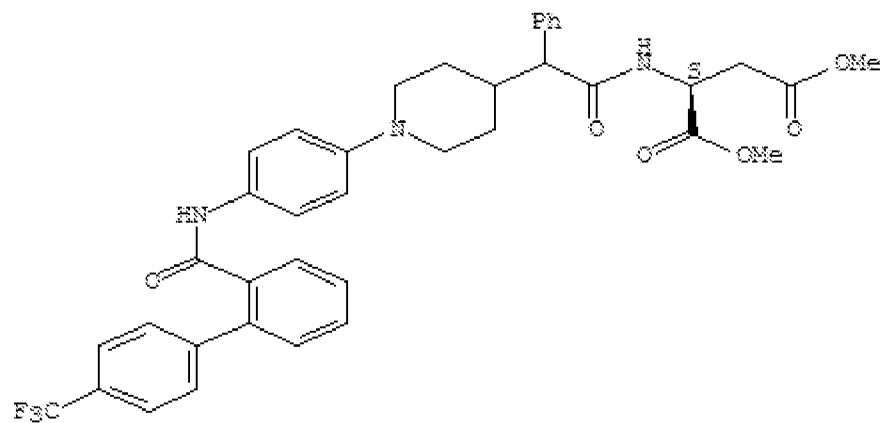
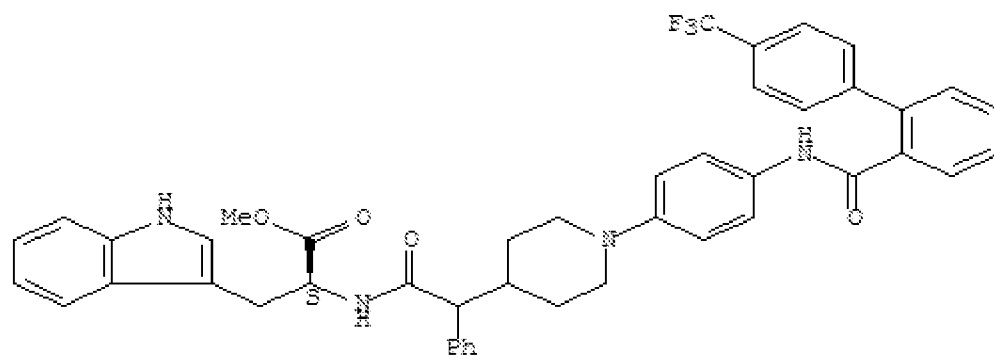
This genus is essentially the same as the instant claims, but PG Pub 2006/0040989 fails to list the specific R5 moieties of the instant claims (i.e. a1 or a2). Meerpoel, WO 2002081460 shows the specific R5 moieties that the instant claims recite., some examples are shown below:



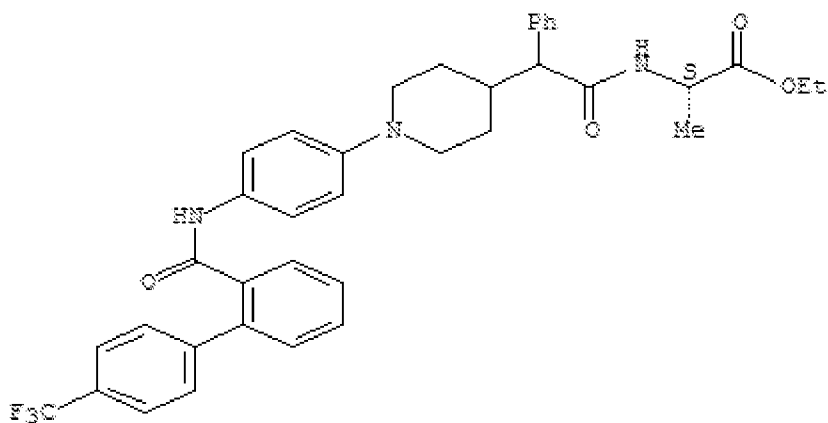
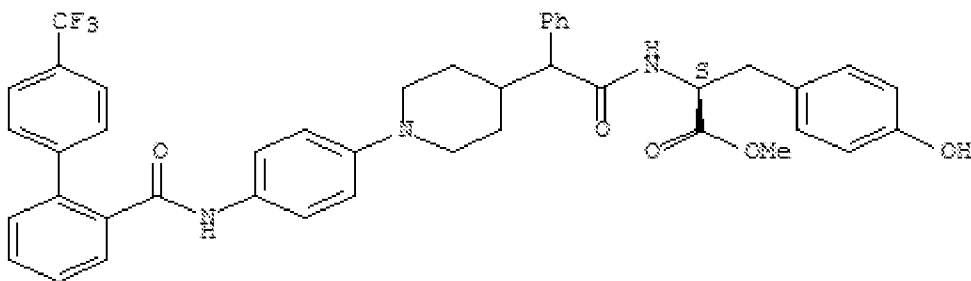
Co. No. 15; Ex. B.5



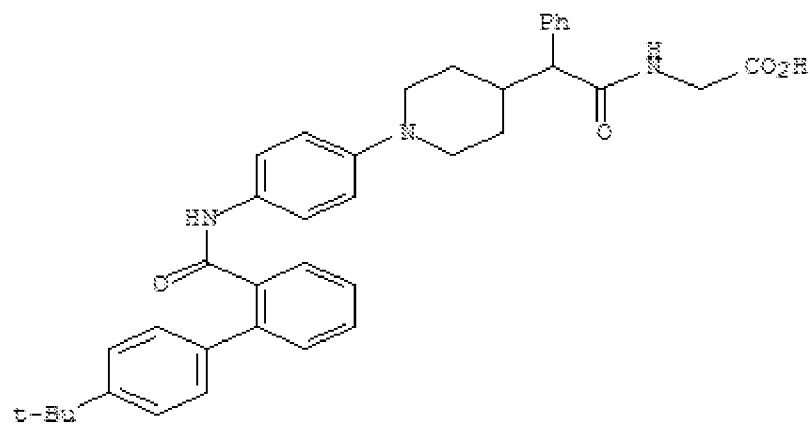
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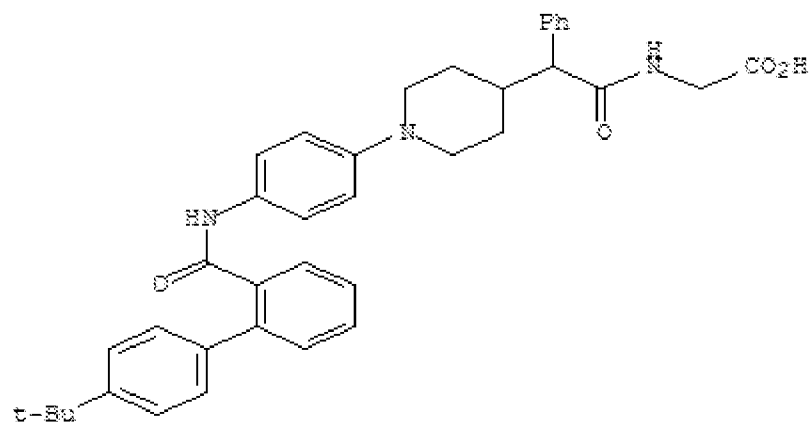
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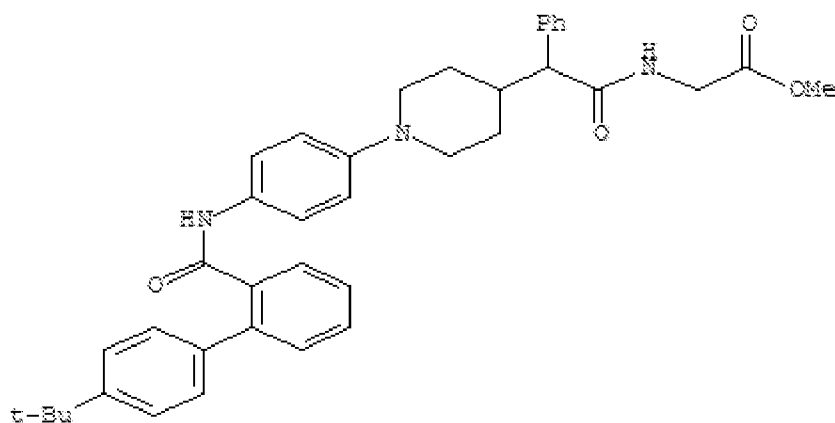
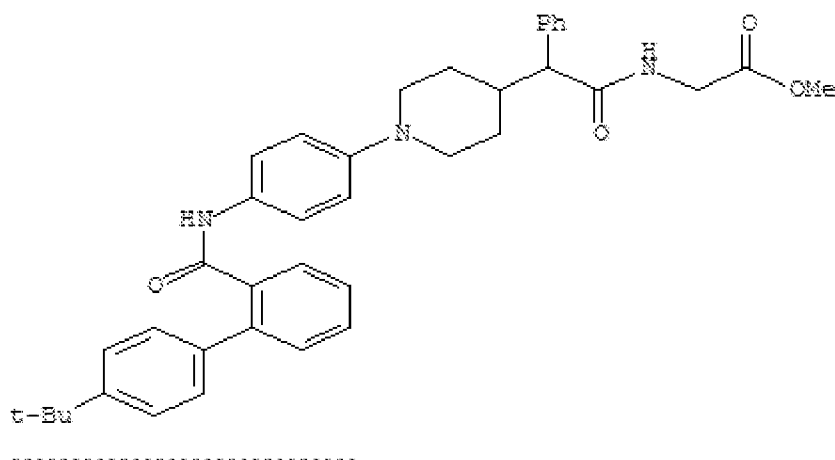


Chemical structure of compound 10



Chemical structure of compound 10

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Ascertainment of the difference between the prior art and the claims

These compounds are inhibitors of MTB, which is the exact same utility of the instant case. The instant claims differ from the prior art by the specific compounds. i.e. the R5

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moiety which is an amino acid moiety.

Resolving the level of ordinary skill in the pertinent art.

The level of ordinary skill is high. Someone preparing these compounds would be trained in organic and medicinal chemistry and would recognize the very close structural similarity and would expect them to have similar properties. It would be routine for a chemist to prepare these species.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

The compounds of the instant case are analogs of old compounds. One of ordinary skill would be motivated to make the compounds of the invention because he would expect the compounds to have similar properties and increased potency and selectivity. Indeed we see that these compounds have similar properties as those described by Shen. *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its **analogs** or isomers, either geometric isomers (*cis v. trans*) or position isomers (emphasis added) (*e.g. ortho v. para*)".

The Williams reference discusses the development of MTP ligands that have substantially the same core, that of a 2-phenylbenzamide, in section 6.2 pg. 482-484. It is clear from this discussion and the drawings of the active compounds, i.e. the structures 7-21, that the key structural feature is a 2-phenylbenzamide, and the other portion may be highly variable. It is very clear based on the teachings of the prior art that the invention is obvious over the prior art.

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Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 10/474,281 in view of in view of Daugan, WO 2003048121 (cited on the IDS), Daugan, WO 2000032582 (U.S. equivalent is 6,552,022), Dodic, WO 2001096327 (cited on the IDS), Daugan, WO 2001097810 in further view of Williams et. al. “Novel Microsomal Triglyceride Transfer Protein Inhibitors” Expert Opinion On Therapeutic Patents 2003, 13, 479-488. The 10/474,281 application is the US case stemming from Meerpoel, WO 2002081460 and the claims are drawn to the compounds as described above in this action at 3. The analysis at 3 applies here.

This is a provisional obviousness-type double patenting rejection.

Conclusion

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6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625